REMARKS

I. Status of Claims

Claims 1-31 are pending in the instant application and generally relate to compounds and methods for the treatment of various conditions and diseases via inhibition of UDP-glucose:N-acylsphingosine glucosyltransferase, or GlcCer synthase, activity.

II. Summary of Rejections

Claims 6, 8, 9, 11, 18, 20-23, 26, and 28-31 stand rejected under 35 U.S.C. § 112, first paragraph, for an asserted lack of enablement commensurate in scope to the claims.

Claims 1-5, 7-17, 19, 20-24, and 27-31 stand rejected under 35 U.S.C. § 112, second paragraph, for various reasons, including the recitation of undefined terms and the use of open-ended ranges.

Finally, claims 12, 13, 24, and 25 stand rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1, 2, and 4 of U.S. Patent No. 6,030,995.

III. The Amendments

Claims 11, 23, and 31 have been amended to clarify the subject matter claimed. In particular, Applicants have substituted the term "obtaining" for the term "recovering" in step a) of these method claims, thereby clarifying that the cells are acquired using any method known in the art. Method claims 6-10, 26-30 and 18-22 have been amended to replace the word "and" with the word "or" prior to the phrase "pharmaceutically acceptable salts thereof."

IV. The rejection of claims 6, 8, 9, 11, 18, 20-23, 26, and 28-31 under 35 U.S.C. §112, first paragraph, should be withdrawn.

Claims 6, 8, 9, 11, 18, 20-23, 26, and 28-31 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way to as to enable one skilled in the art to make and/or use the invention.

At the outset, Applicants respectfully request clarification of the Examiner's comments on page 2 of the Office Action. Specifically, the Examiner asserts that the specification "does not give any guidance as to the full range of diabetic complicating diseases which could be treated . . . ." The pending claims, however, are drawn to compositions and methods of inhibiting cancer cell growth, methods of treating various diseases, methods of reducing tumor angiogenesis, and vaccination methods.

Turning to the merits of the rejection under § 112, first paragraph, for lack of enablement, Applicants respectfully traverse. The enablement inquiry determines whether undue experimentation is required to make and/or use the claimed subject matter and, as noted by the Examiner, this inquiry is guided by a consideration of the factors identified in *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). It is accepted, however, that an application need not teach, and preferably omits, what is well known to those of skill in the art. *Hybritech Inc. v. Monoclonal Antibodies Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986). The present application is directed to "prodrugs of ceramide-like compounds that inhibit glucosylceramide formation." (Specification, page 1, lines 9-10.) As prodrugs, the compounds of the present invention are in an inactive form that can be converted to an active, or drug, form, typically upon introduction into a cell or organism.

Upon conversion to the active drug form, the compounds are known to inhibit glucosylceramide synthase activity. For example, United States Patent No. 6,040,332 ("the '332 patent") expressly teaches that the drugs are "[n]ovel amino ceramide-like compounds [that] inhibit glucosyl ceramide (GlcCer) formation by inhibiting the enzyme GlcCer synthase, thereby lowering the level of glycosphingolipids." ('332 patent, abstract.) The '332 patent further discloses that these drugs "have improved GlcCer synthase inhibition activity and are therefore highly useful in therapeutic methods for treating various conditions and diseases associated with altered glycosphingolipid levels." (*Id.*) The '332 patent exemplifies diseases amenable to such treatment as including cancer and tumorigenic conditions, as well as Tay-Sachs, Fabry's and Gaucher's diseases.

The instant specification effectively combines what is known in the art to a teaching that the aforementioned prodrugs are converted to those active drugs. That conversion is amply taught in the instant specification (*see, e.g.*, Specification at page 5, line 3 to page 8, line 26). Because the prodrugs of the instant application are converted to the drugs described in the art, the scope of infections that could be treated using the prodrug compounds of the present invention is commensurate with the scope of infections that can be treated according to the methods of the '332 patent. Moreover, the express disclosure of suitable disorders in the instant specification is entirely consistent with the knowledge in the art, including disclosure in the instant application of disorders arising from inborn errors of metabolism such as Gaucher, Fabry, Tay-Sachs, Sandhoff and GM1 gangliosidosis (page 9, lines 1-2); disorders involving cell growth and division, such as cancer, collagen vascular diseases, atherosclerosis, and renal hypertrophy of diabetic patients (page 9, lines 21-25); and microbial and viral infections (page 9, line 33 to page 10, line 10). Significantly, however, the prodrug compounds of the present application are not derivable from a knowledge of the known drug compounds, such as those drug compounds recited in the '332 patent.

In view of these general remarks, Applicants now address each of the specific bases for rejecting the claims for asserted lack of enablement. The bases are addressed in the order provided in paragraph 2 the Office Action.

(a) Claims 8, 20, and 28 are enabled by the instant application

Claims 8, 20, and 28 were rejected by the Examiner for an alleged lack of support in the specification "as to the full range of microbial or viral infections that could be treated using the instant claimed process." (Office Action, page 3.) In response, Applicants note that the instant application identifies infections associated with GSLs as suitable for treatment according to the invention, whether that association is due to a requirement for GSL binding by the infectious cell (*e.g.*, a pathogenic bacterium) or virus (*e.g.*, influenza type A), or a requirement for GSL binding by a toxin (*e.g.*, verotoxins) produced thereby, or by another form of association with GSLs. *See, e.g.*, specification, page 9, line 33 to page 10, line 10.

Moreover, the instant specification discloses that the prodrugs disclosed therein are convertible to active "drug" forms suitable for treating microbial and viral infections, and the suitability of using such "drugs" to treat these infections was known in the art (*see, e.g.*, U.S. Patent Nos. 5,916,911 (the "'911 patent"), 5,945,442 (the "'442 patent"), and 6,040,332). Further evidence that glucosylceramide synthase inhibitors are recognized by those skilled in

the art as suitable drugs for the intervention of microbial infections was recently published in a scientific journal (Levery *et al.*, *FEBS Lett.* 525:59-64, 2002, copy attached for the Examiner's convenience). The authors of that publication have confirmed that inhibitors of ceramide glucosyltransferase (namely, D-*threo*-1-phenyl-2-palmitoyl-3-pyrrolidinopropanol (P4) and D-*threo* 3'4'-ethylenedioxy-P4) strongly inhibited spore germination, cell cycle and hyphal growth in fungi. (See abstract). As such, Applicants submit that those of skill in the art would readily recognize that the prodrug compounds of the present invention, which are prodrugs for P4, D-threo 3'4'-thylenedioxy-P4 related compounds also will be effective as antifungal agents. Accordingly, the rejection of claims 8, 20, and 28 under § 112, first paragraph, for lack of enablement has been overcome.

(b) Claims 6, 9-11, 18, 21-23, 26, and 29-31 are enabled by the specification

In this subsection, Applicants respond to the bases for rejection provided in paragraph 2(b)-(d) of the Office Action at pages 3-4 therein. Claims 6, 9-11, 18, 21-23, 26, and 29-31 were rejected by the Examiner on several grounds analogous to the reasons provided for rejecting claims 8, 20, and 28 (see Section (a) above). In particular, the Examiner asserted that "the specification does not reasonably provide enablement for treating all tumors or cancers."

In response, Applicants respectfully traverse and submit that the instant specification discloses that disorders involving cell growth and division, such as cancer, are amenable to treatment with the prodrugs. (Specification, page 9, lines 21-25.) The specification further discloses the suitability of multi-drug resistant tumor cells to the treatment methods of the invention at page 11, line 17 to page 12, line 9. Moreover, Applicants note that the active "drug" compounds corresponding to the prodrugs disclosed in the instant application were known in the art, and the suitability of such active "drug" compounds for treatment of cancer cells and tumor disorders was known in the art. In particular, it was previously established that glucosylceramide synthase inhibitors could be used to treat tumors, as evidenced by the '911 patent and the '442 patent. For example, claims 6, 18, and 26 of the instant application are similar, in relevant part, to methods disclosed and claimed in the '911 patent (*see, e.g.*, claim 1 of the '911 patent, which recites "[a] method for inhibiting the growth of cancer cells in a mammal, wherein said cancer cells are sensitive to the compounds below . . . .").

In addition, claims 9, 10, 21, 22, 29, and 30 are similar, in relevant part, to methods disclosed in the '911 patent and claimed therein. For example, claims 7 and 12 of the '911

patent recite "[a] method for treating a patient having a drug resistant tumor sensitive to the compounds below . . ." and "[a] method for reducing tumor angiogenesis in a patient , wherein said angiogenesis is sensitive to the compounds below . . .," respectively. The instant application teaches one of skill how to convert the inactive prodrugs to the active drug forms in the environments where treatment is expected to be effective. At page 5, line 3, to page 8, line 26 of the instant specification, the application does teach suitable conversions of prodrugs to drugs for the treatment of cancer and/or tumorigenic conditions. Accordingly, Applicants submit that the rejection of claims 6, 9-11, 18, 21-23, 26, and 29-31 under § 112, first paragraph, for an asserted lack of enablement has been overcome.

(c) Claims 11, 23, and 31 are enabled by the specification

In paragraph 2(e) of the Office Action, the Examiner also rejected claims 11, 23, and 31 under 35 U.S.C. § 112, first paragraph, for lack of enablement. In response, Applicants traverse and cite to page 10, lines 11-35 of the specification, which teaches a vaccination method involving the obtaining of cancer cells from a patient using any technique known in the art, exposure of the cells to an inhibitor for a time sufficient to deplete such cells of glycosphingolipids (*i.e.,* GSLs), and reintroduction of such cells into the patient, where the treated cells will exhibit antigenic properties and function as immunogens.

Beyond the fact that instant specification provides explicit guidance to one of skill to use the claimed products in vaccination methods, claims 11, 23, and 31 of the instant application are similar, in relevant part, to vaccination methods taught and claimed in the '442 patent. For example, the '442 patent discloses a vaccination method and claims such a method, with the relevant portion of claim 1 reciting "[a] vaccination method comprising the steps of: a) removing cancer cells sensitive to the compounds below . . . ."

Therefore, Applicants submit that given the teachings of the instant specification in combination with the knowledge of those of skill in the art, one of skill in the art could have used the prodrug agents disclosed in the instant specification in vaccination methods similar to methods already in use in the art. As discussed above, the present specification teaches how to make and use the prodrugs. These prodrugs are convertible to drugs that are acknowledged as being suitable for use in such vaccination methods. As such, following the teachings of the instant application, those skilled in the art would have readily ascertained that the prodrugs would also be suitable for use in such vaccination methods.

(d) Summary remarks on enablement of the pending claims

In view of the state of the art, Applicants submit that there was a high level of predictability in (1) identifying the microbial and viral diseases amenable to treatment with the prodrugs of the present invention, (2) identifying the cancer cells and tumors amenable to treatment, and (3) using a vaccination method, because those therapeutic activities would be the same therapeutic activities known to be useful in treatments involving the corresponding drugs. Thus, the state of the art was relatively advanced and the claimed subject matter did not involve a high level of unpredictability. In terms of related factors, the quantity of experimentation necessary to make and/or use the claimed subject matter was minimal, and that small level of experimentation that might be needed would be routine in nature, and not undue experimentation. Thus, the state of the art, level of predictability, and quantity of experimentation would favor a conclusion that the pending claims were enabled. Also consistent with this conclusion is the guidance provided in identifying and administering the prodrugs such that active drug forms would be produced where needed to effect treatment. Finally, Applicants submit that the level of skill in the relevant field is high, typically involving one having an advanced degree and several years of laboratory or clinical experience. In view of this analysis, Applicants submit that a consideration of the *Wands* factors leads to the conclusion that practice of the presently claimed subject matter would not require undue experimentation. Accordingly, the present application provides an enabling disclosure that is commensurate in scope to the presently pending claims.

For the foregoing reasons, Applicants submit that the rejection of claims 6, 8, 9, 11, 18, 20-23, 26, and 28-31 under 35 U.S.C. § 112, first paragraph, for lack of enablement has been overcome and should be withdrawn.

V. The rejection of claims 1-5, 7-17, 19, 20-24, and 27-31 under 35 U.S.C. §112, second paragraph, should be withdrawn.

Claims 1-5, 7-17, 19, 20-24, and 27-31 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which the Applicants regard as the invention. In response, Applicants traverse.

(a) Claims 1, 12, and 24 are definite

With particular reference to the basis for rejecting claims 1, 12, and 24, the Examiner acknowledged that the R^3 moiety of these claims was defined as a tertiary amine, but the

Examiner maintained that the claims did not specify whether the amine moiety was an aliphatic or heterocyclic amine. In response, Applicants note that the specification defines the R^3 moiety and provides exemplary tertiary amines (*see, e.g.*, page 5, lines 17-19). One of ordinary skill in the art would readily recognize that the specification disclosed a preference, but not a requirement, for a cyclic amine in which the nitrogen atom is attached to the kernel. Thus, the R^3 moiety is a tertiary amine, which may be either aliphatic or cyclic. Given this definition in the specification, there is no indefiniteness in the meaning of the R^3 moiety. Accordingly, this basis for rejecting claims 1, 12, and 24 under § 112, second paragraph, has been overcome and should be withdrawn.

(b) Claims 1 and 12 are definite

The Examiner also supported the rejection of claims 1 and 12 under § 112, second paragraph, by asserting that the specification failed to identify what moiety is being hydrolyzed with respect to R^4. The R^4 moiety itself is expressly defined in the specification (page 5, lines 20-22) as any group that is selectively hydrolyzable in a target cell. Immediately thereafter, the specification recites that "[t]he compounds of the present invention are converted in the cell to the active, inhibitory forms of the compounds having the general formula: . . . ." (Specification, page 5, lines 23-24.) The structure immediately following the colon contained in the preceding quote is identical to the structure illustrative of the compounds of the invention that is provided at page 5, lines 4-5, with the exception that a hydroxyl hydrogen atom is substituted for R^4. This disclosure unambiguously identifies the entire R^4 moiety as being separated from the remainder of the molecule during the process of hydrolysis.

Still further, the specification states that "the prodrugs of the present invention comprise a covalently attached hydrolyzable group (R^4) to the hydroxyl of the 1-propanol backbone that is selectively hydrolyzed within the cell, preferably enzymatically. The chemical moeity [sic] can be any group that is selectively hydrolyzed to produce an active compound with a unmodified hydroxyl in the cell." (Specification, page 6, lines 14-18.) Thus, one of ordinary skill in the art would recognize that R^4 is a pro-group (a hydrolyzable group) that is eliminated *in toto* by hydrolyzing it from the remainder of the pro-drug compound. Thus, it is the R^4 group itself that is being lost from the remainder of the pro-drug (*i.e.*, the drug) by hydrolysis.

The Examiner also asserted that the identification of the target cell recited in claims 1 and 12 was unclear. In response, Applicants note that the instant specification teaches that target cells having altered GSL levels will convert the prodrugs to active drugs capable of modulating the GSL levels in those target cells. Thus, the specification identifies target cells as those cells having altered GSL, or GSL precursor, levels. Exemplary target cells are those cells involved in disorders such as those of Gaucher, Fabry, Tay-Sachs, Sandhoff and GM1 gangliosidosis (page 9, lines 1-2); disorders involving cell growth and division, such as cancer, collagen vascular diseases, atherosclerosis, and renal hypertrophy of diabetic patients (page 9, lines 21-25); and cells susceptible to microbial and/or viral infections (page 9, line 33 to page 10, line 10). The identification of target cells in the instant specification, moreover, is entirely consistent with the knowledge in the art of those cells exhibiting altered GSL or GSL precursor levels that are associated with known diseases or disorders characterized by just such a feature.

(c) Claims 3, 14, and 15 are definite

Claims 3, 14, and 15 were rejected for failing to set an upper limit for the value of n. In response, Applicants submit that there is no ambiguity or indefiniteness in defining a chemical structure using an open-ended range for repeating subunits. This convention is required to properly define the full scope of polymeric chemicals. Accordingly, Applicants submit that the claims as filed are not indefinite and that this ground for rejecting claims 3, 14, and 15 under § 112, second paragraph, has been overcome.

(d) The rejection of claim 24 is definite

In support of the rejection of claim 24 under 35 U.S.C. § 112, second paragraph, the Examiner asserted that the claim failed to describe the value of the variable n. In response, Applicant's cite to the specification at page 8, line 10, wherein the variable n is defined as "an integer from about 1 to about 19." Thus, the value of the variable n is adequately described in the specification as filed. Accordingly, claim 24 is definite and the rejection of that claim under § 112, second paragraph, has been overcome.

(e) Claims 8-10, 20-22, and 28-30 are definite

In paragraph 3(e)-(g), claims 8, 20, and 28 were rejected under § 112, second paragraph, for failing to define what kind of infection the Applicants are intending to treat; claims 9, 21, and 29 were rejected for failing to describe the type of tumor or cancer to be treated; and claims 10, 22, and 30 were rejected for failing to describe a specific type of

tumor. In response, Applicants refer to the remarks made above in the context of addressing the enablement issue and incorporate those remarks herein as though set out in full. In particular, Applicants again note the knowledge in the field, as revealed by the disclosures of the '332, '911, and '442 patents. Such information, known in the art, need not be disclosed and is preferably omitted from the specification. Moreover, the instant specification identifies infections associated with GSLs as suitable for treatment according to the invention, whether that association is due to a requirement for GSL binding by the infectious cell or virus, or a requirement for GSL binding by a toxin produced thereby, or by another form of association with GSLs. *See, e.g.,* specification, page 9, line 33 to page 10, line 10. Further, the specification defines the tumor or cancer cells as those cells characterized by an altered GSL or GSL precursor level, including, *e.g.*, multi-drug resistant tumor cells. *See* specification, page 9, lines 11-25.

(f) Claims 11, 23, and 31 are definite

Support for the rejection of claims 11, 23, and 31 under § 112, second paragraph, was provided in the Examiner's assertion that the claims were being vague and indefinite in reciting the phrase "removing cancer cells . . . ." The Examiner asserts that it is unclear how Applicants are intending to remove the cells and from what location. In response, Applicants submit that one of skill in the art would know how to obtain the cells and from where they should be obtained, and this position is supported by the disclosures in issued U.S. Patent No. 5,945,442 (*see, e.g.*, claim 1 therein). Without altering the scope of any claim, Applicants have amended claims 11, 23, and 31 by replacing the term "removing" with the term "obtaining", thereby clarifying the subject matter of each of these claims. The Applicants submit that obtaining cells (*e.g.,* cancer cells) from a patient is routinely practiced by one of ordinary skill in the relevant art of medicine. Thus, the present amendment obviates the Examiner's rejection without altering the scope of any one of claims 11, 23 or 31.

(g) Claims 2, 4, 5, 7, 13, 16, 17, 19, and 27 are definite

In paragraph 4 of the Office Action, the Examiner rejected claims 2, 4, 5, 7, 13, 16, 17, 19, and 27 under 35 U.S.C. §112, second paragraph, as being dependent on rejected base claims. In response, Applicants submit that the present amendment overcomes each one of the rejections of the relevant base claims, thereby obviating the instant rejection.

VI. The rejection of claims 12, 13, 24 and 25 under the judicially-created doctrine of obvious-type double patenting.

The Examiner rejected claims 12, 13, 24 and 25 under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, and 4 of U.S. Patent No. 6,030,995. Specifically with regard to instant claims 12 and 13, the Examiner asserted that when R^4 is H, these claims are drawn to the same compound as claim 1 of the '995 patent when R^1 is a hydroxy-, methoxy-, etc. substituted phenyl group. (Office Action at page 7).

While Applicants initially disagree with the Examiner that the instant claims are obvious over the '995 patent, Applicants respectfully request that the issue of obviousness-type double patenting be held in abeyance until such a time as Applicants have received an indication that the claims are otherwise in condition for allowance. At that time, Applicants will furnish the appropriate remarks to distinguish the allowed claims over the disclosure of the '995 patent or present a terminal disclaimer depending on which measure is appropriate to facilitate issuance of the claims. Applicants respectfully request the Examiner's discretion in this matter.

VII. CONCLUSION

For the foregoing reasons, Applicants respectfully submit that the rejections of claims 1-31 have been overcome and the claims are now in condition for allowance.

Respectfully submitted,

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